

Supplementary Online Content

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Supplement 3. eAppendix

This supplementary material has been provided by the authors to give readers additional information about their work.

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This appendix has been provided by the authors to give readers additional information about the trial.

Effect of peroral endoscopic myotomy versus pneumodilation on symptom severity and treatment outcomes among treatment-naïve patients with achalasia: a randomized clinical trial

26 **eAppendix**

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51 **Abbreviations:**

52 GERD-Q – Gastroesophageal reflux disease questionnaire

53 HRM – High-resolution manometry

54 IQR – Interquartile range

55 IRP – Integrated relaxation pressure

56 LES – Lower esophageal sphincter

57 POEM – Peroral endoscopic myotomy

58 PPI – Proton pump inhibitors

59 SAE – Serious adverse event

60 SD – Standard deviation

61 TBE – Timed barium esophagogram

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76 **1. Interventions**

77 *1.1 Peroral endoscopic myotomy*

78 Peroral endoscopic myotomy (POEM) was carried out under general anesthesia with
79 endotracheal intubation. The procedure was then performed as described by Inoue et
80 al.¹ A forward viewing upper endoscope (GIF H180J; Olympus, Hamburg, Germany)
81 with a transparent distal cap (MH 588; Olympus or Fujifilm) was used. Carbon dioxide
82 gas was used for insufflation during procedures. An endoscopic knife (KD-640L
83 TriangleTipKnife: Olympus) was used to access the submucosa, create the
84 submucosal tunnel and divide the circular muscle layer in the distal esophagus and
85 2-3 cm onto the cardia, including cutting the lower esophageal sphincter (LES). An
86 electrogenerator (Erbe Vio 300D; Erbe Elektromedizin, Tübingen, Germany) was
87 used to open the mucosa and the spray coagulation mode was selected to dissect
88 the submucosa and cut the muscle fibers. The mucosal entry site was closed by
89 standard endoscopic clips (HX-110UR EZ Clip Reusable Rotatable Clip Fixing
90 Device and HX-610-135L Single Use Clips; Olympus).

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92 **2. Adverse events**

93 *2.1 Definition of serious/severe and mild adverse events*

94 Adverse events were defined as any unwanted event that occurred following the
95 study treatment, secondary to the study treatment or unrelated to study treatment
96 during follow-up. Adverse events were defined as severe (serious) based on the
97 following criteria

- 98 - Unexpected hospital admission for >24 hours or prolongation of a planned
- 99 hospital admission for >24 hours related or unrelated to the study treatment
- 100 - Admission to a medium or intensive care related to the study treatment

- 101 - Additional endoscopic procedures within 24 hours after the study treatment
- 102 - Need of blood transfusion after the study treatment
- 103 - Death, related or unrelated to the study treatment

104 Adverse events not fulfilling the above described criteria were classified as mild.

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106 **3. Results**

107 *3.1 Serious adverse events independent of study intervention*

108 One patient in the pneumodilation group developed a herpes encephalitis with a
109 bilateral thalamus infarct and post-treatment had severe lateralization and aphasia.
110 Consequently, further follow-up according to study protocol was not possible. This
111 patient had recurrent symptoms at 1-year follow-up even before the SAE occurred
112 and was already considered a treatment failure. Three patients had a myocardial
113 infarction during the study period, two in the pneumodilation group and one in the
114 POEM group, these were deemed to be unrelated to achalasia or its treatment. All
115 three patients could continue the study follow-up. One patient was diagnosed with a
116 renal cell carcinoma that was treated by nephrectomy. This patient was treated by
117 pneumodilation and could continue study follow-up.

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129 **Supplementary Appendix tables and figures**

	POEM (N=63)		Pneumodilation (N=63)		<i>p</i> *
Treatment failures 2-year follow-up (n and % (SD))	5/63	8 (3.4)	29/63	46 (6.3)	<.001
Type of retreatment (n (%))					-
Pneumodilation 30 mm	1 (20)		-		
Pneumodilation up to 35 mm	2 (40)		3 (10)		
Pneumodilation up to 40 mm	1 (20)		11 (38)		
Pneumodilation up to 40 mm + POEM	-		9 (31)		
Pneumodilation up to 40 mm + laparoscopic Heller myotomy	1 (20)		-		
POEM	-		2 (7)		
Laparoscopic Heller's myotomy	-		1 (4)		
None / unknown	-		3 (10)		
Total number of treatments including retreatment (n)	75		162		<.001
Overall treatment success including pneumodilation 40 mm (n and % (SD))	58/63	92 (3.4)	48/63	76 (6.4)	0.008

130 **eTable 1. Overview of type of retreatment after treatment failure and the**
 131 **additional effect of the pneumodilation 40 mm on treatment success.**

132 Data are presented as numbers (n) or percentages (SD). *Chi-square.

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<u>Primary outcome per-protocol</u>		POEM		Pneumodilation		Unadjusted absolute difference (95% CI)	Risk ratio (95% CI)	<i>p</i> *
2-year follow-up (primary endpoint)								
Overall treatment success (n and % (SD))	58/63	92 (3.4)	31/58	53 (6.6)		39 (22, 53)	1.72 (1.34, 2.21)	<.001
3 months follow-up (secondary endpoint)								
Overall treatment success (n and % (SD))	63/64	98 (1.8)	47/60	78 (5.3)		20 (8, 33)	1.26 (1.10, 1.44)	<.001
1-year follow-up (secondary endpoint)								
Overall treatment success (n and % (SD))	61/64	95 (2.7)	38/59	64 (6.3)		31 (16, 45)	1.48 (1.34, 2.21)	<.001

136 **eTable 2. Primary outcome per-protocol analysis at 2 years, 3 months and 1-year of follow-up according to type of**
 137 **treatment.**

138 Data are presented as numbers (n), percentages (SD) or absolute difference (95% CI). *Chi-square.

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Secondary outcome 3 months follow-up	POEM (N=63)	Pneumodilation (N=52)	Unadjusted absolute difference (95% CI)[*]	p^{**} (post-hoc p) ^{***}
Eckardt score (median (IQR)) ^a	1 (0-2)	1.5 (1-2)	0.5 (0, 1.5)	0.009 (0.09)
Integrated relaxation pressure (mmHg; median (IQR))	8.7 (5.4-14.3)	11.8 (7.7-14.3)	3.1 (0.1, 6.1)	0.13 (0.99)
Basal LES pressure (mmHg; median (IQR))	11.7 (7.2-15.8)	12.1 (8.9-19.9)	0.4 (-4.6, 5.4)	0.45 (0.99)
Barium column height (cm; median (IQR))	0 (0-2)	0 (0-3.7)	0 (-1.1, 1.1)	0.47 (1.0)
Barium column diameter (cm; median (IQR))	2.1 (1.9-2.7)	2.3 (1.9-2.8)	0.2 (-0.1, 0.5)	0.7 (1.0)
Achalasia DSQoL (median (IQR)) ^b	12 (11-15)	13 (11-16)	1 (-1, 3)	0.08 (0.72)
GERD-Q (median (IQR)) ^c	6 (6-7)	6 (6-8)	0 (0, 0)	0.84 (0.84)
GERD-Q ≥8 (% (SD)) ^c	21 (5.1)	27 (6.2)	6 (-11, 23)	0.43 (0.97)
SF-36 (median (IQR)) ^d				
Physical Component Summary Score	55.4 (50-58.6)	54.9 (44.1-57.9)	0.5 (-3.4, 4.4)	0.3 (0.99)
Mental Component Summary Score	53.6 (46.9-57.8)	54.5 (47.6-56.5)	0.9 (-8.7, 10.5)	0.84 (0.84)
Secondary outcome 1 year follow-up	POEM (N=61)	Pneumodilation (N=42)	Unadjusted absolute difference (95% CI)[*]	p^{**} (post-hoc p) ^{***}
Eckardt score (median (IQR)) ^a	1 (0-2)	1 (0-2)	0 (-1, 1)	0.98 (0.98)

Secondary outcome 1 year follow-up	POEM (N=61)	Pneumodilation (N=42)	Unadjusted absolute difference (95% CI)*	p** (post-hoc p)***		
Integrated relaxation pressure (mmHg; median (IQR))	9 (6.6-15.4)	11 (8.6-15.6)	2 (-0.5, 4.5)	0.83 (1.0)		
Basal LES pressure (mmHg; median (IQR))	13.9 (8.1-18.5)	14.7 (10.6-26)	0.8 (-1.9, 3.5)	0.11 (0.88)		
Barium column height (cm; median (IQR))	1.7 (0-3.3)	0 (0-2.4)	1.7 (-0.8, 4.2)	0.1 (0.90)		
Barium column diameter (cm; median (IQR))	2.5 (2.1-3)	2.1 (1.6-2.6)	0.4 (-0.6, 1.4)	0.004 (0.05)		
Achalasia DSQoL (median (IQR)) ^b	14 (11-17)	13 (11-15)	1 (-1, 3)	0.29 (0.99)		
GERD-Q (median (IQR)) ^c	6 (6-8)	6 (6-7)	0 (-1, 1)	0.03 (0.36)		
GERD-Q ≥8 (% (SD)) ^c	30 (5.9)	16 (5.7)	14 (-6, 24)	0.11 (0.99)		
SF-36 (median (IQR)) ^d						
Physical Component Summary Score	53.5 (49.1-57.8)	54.2 (51.3-56.8)	0.7 (-1.6, 3)	0.38 (1.0)		
Mental Component Summary Score	54.4 (50.5-57.7)	53.5 (47.3-56.1)	0.9 (-1.1, 2.9)	0.27 (1.0)		
Endoscopic reflux esophagitis (n and % (SD))	29/59	49 (6.5)	4/36	11 (5.2)	38 (17, 53)	<.001 (<.001)
Grade A (n (%))	15 (26)		1 (3)			
Grade B (n (%))	9 (15)		3 (8)			
Grade C (n (%))	3 (5)		0 (0)			
Grade D (n (%))	2 (3)		0 (0)			

Secondary outcome 1 year follow-up	POEM (N=61)		Pneumodilation (N=42)		Unadjusted absolute difference (95% CI)*	p** (post-hoc p)***
PPI use (n and % (SD))	14/61	23 (5.4)	6/42	14 (5.4)	9 (-8, 24)	0.28 (0.98)
Reflux esophagitis (n (%))		8 (57)		1 (17)		
No reflux esophagitis (n (%))		6 (43)		5 (83)		

144 **eTable 3. Secondary outcomes at 3 months and 1-year of follow-up according to type of treatment.**

145 Data are presented as numbers (n), percentages (SD), median (IQR) or absolute difference (95% CI). * Absolute difference of the median or proportion **Mann-Whitney or Chi-
 146 square. ***p adjusted for multiple comparison.

147 ^aEckardt score: achalasia symptoms, range 0-12, highest score indicated most pronounced symptoms.

148 ^bAchalasia-DSQoL: quality of life related to achalasia, range 10-33, lower score indicated better quality of life.

149 ^cGERD-Q: gastroesophageal reflux disease, range 0-18, score ≥8 was highly suggestive for presence of GERD.

150 ^dSF-36: general quality of life consisted of Physical Component Summary Scale, range 0-100, and Mental Component Summary Scale, range 0-100, higher score indicated
 151 better quality of life.

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Primary outcome 2-year follow-up	Adjusted odds ratio (95% CI)	p
Treatment*	22.2 (4.69-105.4)	<.001
Achalasia subtype		0.33
Subtype I	2.41 (0.76-7.65)	0.14
Subtype II**	1.0	
Subtype III	1.1 (0.20-6.22)	0.91
Achalasia subtype x POEM		0.35
Subtype I	0.19 (0.01-2.96)	0.23
Subtype II**	1.0	
Subtype III	0.20 (0.01-3.04)	0.25

160 **eTable 4. Logistic regression analysis of the primary outcome (treatment**
 161 **success) in relation to treatment, subtype and treatment x subtype interaction.**

162 * Pneumodilation served as the reference category

163 **Served as the reference category.

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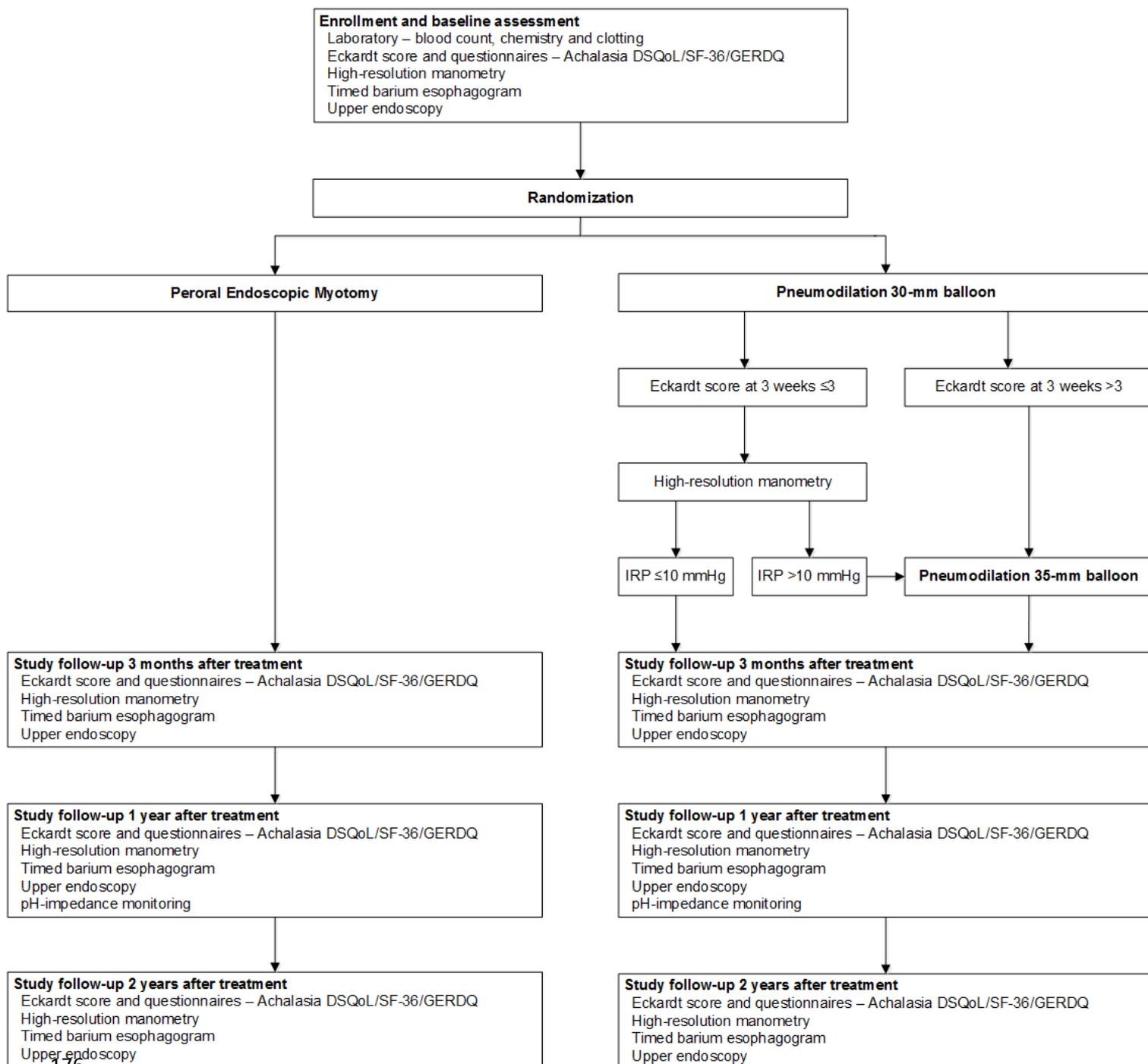
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178 **eFigure 1. Treatment and study follow-up algorithm for POEM and pneumodilation.**

179 After the first pneumodilation with a 30-mm balloon the effect was evaluated by the Eckardt
 180 score at 3 weeks. A second pneumodilation with a 35-mm balloon was performed in case the
 181 Eckardt score was >3 or ≤3 with an IRP >10 mmHg.

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185 **eAppendix references**

- 186 1. Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM)
187 for esophageal achalasia. *Endoscopy*. 2010;42:265–271.

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